SPECIFIC AIDS IN THE DIAGNOSIS AND PROGNOSIS OF TUBERCULOSIS.[1]

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I purpose to consider the relative value of specific aids in the diagnosis and prognosis of tuberculosis; first, of tuberculin in its various methods of application, and second, of the serum reactions and particularly the agglutinin reaction, in the light of my own investigations as compared with those of other observers.

With the introduction of tuberculin a most valuable aid was afforded in determining the presence or absence of tuberculous affections in doubtful cases, and increased interest in the subject was actively aroused by the almost simultaneous and independent communications of Wolff-Eisner[2] and Calmette[3] of their conjunctival method, and of von Pirquet's[4] cutaneous method of applying tuberculin for diagnostic purposes.

From the literature I have collected a large number of results of the use of the subcutaneous, cutaneous, and conjunctival methods respectively.[5] From a tabulation of these results, it appears that by the subcutaneous method, among 7088 cases tested there were 4805 tuberculous, in 4319 of which the reaction was positive; 479 suspects, with 313 positive reactions; and 2804 non-tuberculous cases, in 1440 of which positive reactions occurred. By the conjunctival method, among 6449 cases tested, there were 2734 tuberculous, in 2164 of which reaction was positive; 1188 suspects, with 687 positive; and 2527 non-tuberculous subjects, with 347 positive reactions. By von Pirquet's cutaneous method, among 6504 cases tested there were 2182 tuberculous, with 1861 positive reactions; 815 suspects, with 550 positive reactions; and 3507 non-tuberculous subjects, in 1109 of whom the reaction was positive. The latter figures include results in 900 non-tuberculous children, of whom 149 had reacted positively. Excluding these cases, there are positive results in 1060 out of 2607 non-tuberculous adults.

The percentages of cases in which positive reactions followed the application of the tests were, respectively:

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[1] Read by title at the International Congress on Tuberculosis, Washington, D. C., October 3, 1908.

[2] Berl. med. Ges., May 15, 1907. Discussion zu v. Pirquet's Vortrag., Berl. klin. Woch., 1907, xliv, 700.; Beitr. z. Klin. d. Tuberk., 1908, ix, 1.

[3] Presse médicale, June 19 and July 13, 1907 (cf. Zentrlbl. f. Chir., 1907, xxxiv, 1031).

[4] Berl. med. Ges., May 8, 1907 (cf. Berl. klin. Woch., 1907, xliv, 644, 700); Wien. med. Presse, 1907, xlviii, 155; Kutane und konjunktivale Tuberkulinreaktion, in Krause and Levaditi, Immunitätsforchung, Jena, 1908, l, 1035 (1042); Wien. klin. Woch., 1907, xx, 1123; 1908, xxi, 623.

[5] Owing to lack of space, it has been necessary to omit this and all other tabulations prepared for this paper. The literature has been considered up to July, 1908.

	Tuberculous. Per. cent.	Suspects. Per cent.	Non-tuberculous. Per cent.
Subcutaneous	89.88	63.34	51.30
Conjunctival	79.20	57.80	13.73
Cutaneous	85.29	67.48	31.62
		Exclusive of children,	40.66

At the Winyah Sanitarium tuberculin has been injected for diagnostic purposes since 1891 in 300 cases, with positive reactions in 75 per cent. at a period of the disease in which tubercle bacilli were absent from the sputum or in which there was no expectoration. The conjunctival method has been applied in 127 cases, 101 tuberculous and 26 non-tuberculous. Of the tuberculous, 23 were cured or arrested cases which had been treated specifically and discharged from one to ten years previously, and whose health had remained good. Thirty-four were, at the time, under treatment with specific remedies; the additional 44 cases were tested on admission to the institution, and had not been so treated.

For the tests, solution of the alcoholic precipitate of tuberculin prepared, according to Calmette's formula, from tuberculin from human tubercle bacilli, was used, and also an identical preparation from bovine bacilli.

Of the 23 cured and arrested tuberculous cases, none reacted to instillations of human purified tuberculin into the right eye. In 16 of these, bovine tuberculin was instilled into the left eye; 9 failed to react, in one there was a trace, in 4 the reaction was positive in the first degree, in one in the second degree, and in the other, in which there was a chronic conjunctivitis, a severe third-degree reaction accompanied by fever occurred. This latter case, however, failed to react to cutaneous application of human tuberculin. All these patients had been treated with specific products of human tubercle bacilli.

Of the 34 cases in which the test was made while under specific treatment, instillations of human purified tuberculin were made in the right eyes of 33. There was no reaction in 18, while in 15 the reaction was positive—slight in 9, of the first degree in 4, and of the second degree in 2. Of the 18 cases which failed to react to instillations of human purified tuberculin into the right eye; 14 received purified bovine tuberculin into the left eye, with positive results in 11, while 3 proved negative to both preparations. Of 12 cases which had reacted positively to human, 11 reacted also to bovine tuberculin in the other eye. Of the 44 tuberculous patients who had received no specific treatment, 28, or 63.64 per cent., reacted positively to first instillations of human tuberculin in the right eye. Two additional cases reacted to a second instillation of the same preparation in the same eye. The remaining 14 were negative. Of the same 44 cases, 30 received also instillations of bovine tuberculin in the left eye. Of these 30, the reaction was positive to both preparations in 14, negative to both in 7, positive to human but negative to bovine tuberculin in 2, negative to human but positive to bovine tuberculin in 7, to the first instillations respectively. Deducting the 7 cases in which neither preparation caused reaction, there is a total of 37 (84.09 per cent.) in which the reaction was positive.

There remain for consideration the 26 non-tuberculous cases, all of which were in good health and free from suspicion of infection. None reacted to instillations of human tuberculin into the right eye; 10 received second and third instillations with solutions up to 4 per cent. in strength of this preparation into the same eye, with entirely negative results. Bovine tuberculin in 1 per cent. solution was also instilled into the left eye of 18, likewise with negative results.

Cohn,[6] Fritz Levy,[7] Klieneberger,[8] Schenck and Seiffert,[9] Rosenau and Anderson[10] and others have found that clinically non-tuberculous persons react to second or third instillations of tuberculin into the same eye after previous instillations have been negative. It has therefore been objected that such repeated applications cause local hypersensitiveness of the conjunctiva, and thus render the reaction of no clinical value. Roepke,[11] however, denies that in persons free from tuberculosis repeated instillations into the same eye cause reaction, and, moreover, insists that only such repeated instillations of tuberculin, in solutions up to 4 per cent., are sufficient to cause reaction in all active tuberculoses. The negative results of repeated instillations reported by Smithies and Walker,[12] and my own experience in the ten cases already mentioned, incline me to Roepke's view, but the question requires further investigation.

It is of interest to note that the percentages of positive reactions to the first instillation of human tuberculin in my own tuberculous cases bear a very evident relation to the employment of specific medication:

	Per cent.
Of 44 untreated cases, the reaction was positive in	63.64
Of 34 cases under treatment, the reaction was positive in	44.1
Of 18 cases under treatment for six months or longer, the reaction was positive in	27.77
Of 23 cured or arrested cases which had received specific treatment, the reaction was positive in	None

Such an influence has been observed by others also. Mitulescu[13] reports six cases treated specifically and apparently cured, in all of which reaction was negative, and like experiences are recorded by

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[6] Berl. klin. Woch., 1907, lxiv, 1507.

[7] Deut. med. Woch., 1908, xxxiv, 94.

[8] Ibid., 777; Münch. med. Woch., 1907, liv, 2588.

[9] Münch. med. Woch., 1907, liv, 2269.

[10] Jour. Amer. Med. Assoc., 1908, l, 961.

[11] Beitr. z. Klin. d. Tuberkulose, 1908, ix, 353.

[12] Jour. Amer. Med. Assoc., 1908, l, 259.

[13] Wien. klin. Woch., 1908, xxi, 727; Deut. med. Woch., 1903, xxix, 367).

Schultz-Zehden,[14] King,[15] Citron,[16] Lenhartz,[17] Damask,[18] and others. The fact that patients while under specific treatment, as will be shown later, acquire a progressive increase of their serum-agglutinating power, and that the specific amboceptor becomes likewise present in greater quantitative degree, would seem to indicate that, as specific resistance to the pathogenic action of the tubercle bacillus increases, patients react to tuberculin with less and less frequency, and finally not at all.

It may, therefore, be asserted, that the conjunctival tuberculin test may supply the final proof of a cure, just as subcutaneous injections of tuberculin have been administered for the same purpose. In a former publication jointly with Dr. Karl von Ruck[19] I have called attention to the value of the tuberculin test in this respect, which Heron[20] considers as a corollary to the diagnostic value of tuberculin.

The test has also thus been employed by Bandelier,[21] Holdheim,[22] and by Mitulescu, who considers as actually cured only such cases as fail to react to tuberculin. Further prognostic inferences I have been unable to draw from my own studies thus far, and I have not observed any apparent relation between the degree of reaction to either the conjunctival or the cutaneous test and the severity or extent of the disease, which would lead to the modification of a prognosis based upon other considerations. Therefore, like Klieneberger, Schroeder and Kaufmann,[23] and especially Roepke, I cannot subscribe to the opinions expressed by Stadelmann and Wolff-Eisner,[24] Damask, Heinemann,[25] and Fritz Levy in this respect.

Cutaneous tuberculin tests have also been made at the Winyah Sanitarium in 107 cases, both human and bovine tuberculin having been employed in nearly all. Of 67 clinically tuberculous patients tested with human tuberculin in 50 per cent. solution, a positive reaction occurred in 44, in 4 the reaction was doubtful, and in 19 the result was negative. Of these 67 cases, 60 were also tested with bovine tuberculin in 50 per cent. solution; 24 gave a positive reaction, in 1 the reaction was doubtful, in 35 it was negative. Between the two tests in most cases about two weeks elapsed, the human tuberculin having been employed first. The above cases were in most instances receiving specific treatment when the tests were made.

Of 16 cured cases in which the tests were applied simultaneously (that is, human and bovine tuberculin), 12 reacted positively to a 50 per cent. solution of human tuberculin, 1 was doubtful, and 3 were negative. To the bovine tuberculin 9 gave a positive and 7 a negative reaction. Of 24 clinically non-tuberculous persons, mostly tested simultaneously with both preparations, 12 gave a positive result, in the case of human tuberculin, 1 gave a late reaction (three days), 11 were negative. To the bovine tuberculin 6 gave a positive reaction and 18 were negative.

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[14] Therapeut. Monatsh., 1908, xxii, 177.

[15] Medical Record, 1907, lxxii, 976.

[16] Berl. klin. Woch., 1907, xliv, 1052; Deut. med. Woch., 1908, xxxiv, 316.

[17] Münch. med. Woch., 1907, liv, 2404.

[18] Wien. klin. Woch., 1908, xxi, 121.

[19] A Clinical Study of 261 Cases of Pulmonary Tuberculosis, Asheville, N. C., 1905, p. 17; Journal of Tuberculosis, 1899, i, 179.

[20] Transactions of the British Congress on Tuberculosis, 1901, London, 1902, iii, 84.

[21] Deut. med. Woch., 1902, xxviii, 357.

[22] Berl. klin. Woch., 1904, xli, 1040.

[23] Münch. med. Woch., 1908, lv, 62.

[24] Deut. med. Woch., 1908, xxxiv, 227.

[25] Münch. med. Woch., 1908, lv, 556.

In the entire material there were only 4 second degree reactions to human tuberculin, and 3 to bovine. In general the reactions were very mild. In one case classed as "cured," in which 1 per cent. bovine purified tuberculin was instilled into the left eye at the same time at which both cutaneous tests were made, the temperature rose to 100.2° F. the next day. The reactions persisted for several days, up to one week, pigmentation being visible for several weeks after vaccination.

My own experience, like that of many others, has been that the respective results are often contradictory and warrant no definite conclusions. It should be mentioned, however, that, with two exceptions, those tested were all adults, for whom v. Pirquet himself asserts the method to be unreliable. With Detre's[26] modification, which consists in substituting the filtrates of respectively human and bovine cultures for the concentrated tuberculin, and by the reaction to which he claims to differentiate the type of infection, I have had no experience. Neither have I tested any patients after Moro's[27] and Lignière's[28] methods.

The specific nature of both the conjunctival and the cutaneous tuberculin reactions has been denied by various writers, for reasons similar to those some years ago alleged in evidence that the reactions induced by subcutaneous injection of tuberculin should not be so considered.

For all three methods it has been objected that reactions occur in health and in other diseases, notably in typhoid fever. Of 70 cases of the latter affection which I have found in the literature, positive reactions followed conjunctival instillations of tuberculin in 20, or 28.57 per cent. I shall enter into the question of the reaction in typhoid fever patients more fully when considering the serum reactions. Suffice it to say that these apparent contradictions can neither militate against the specific nature of tuberculin reactions nor minimize their diagnostic value, since the percentage of positive results is quite generally in harmony with autopsy findings of tuberculosis in the clinically non-tuberculous, and not only in the adult, but it also corresponds very closely in children to the frequency of infection as shown postmortem with advancing age.

[26] Wien. klin. Woch., 1908, xxi, 173.

[27] Münch. med. Woch., 1908, lv, 216.

[28] Recueil d. méd. vétér., etc., 1907, lxxxiv, 514 (cf. Zentralbl. f. Bakt., Ref. 1908, xlI, 81).

Thus Schreiber[29] reported, in 1891, subcutaneous injections of tuberculin, even up to 10 mg. as an initial dose, in 40 newborn children, with negative results in all. By Binswanger[30] 261 children under one year of age were injected, with positive reactions in 35, or 13 per cent. Forty-two of these children came to autopsy; 16 of them had reacted positively, and all these were found tuberculous. Of the 26 remaining children who had not reacted, 25 were found to be free from tuberculosis.

According to the conjunctival tuberculin test practised in 294 children, Ausset[31] has also confirmed in general the findings as to frequency of tuberculosis in childhood. The percentage of positive reactions rises gradually after the first three months of life, as is shown in the following table:

13	children,	0 to 3 months	0, or 0.01	per cent.
53	"	0 to 1 year	8, or 15.09	"
31	"	1 to 2 years	7, or 22.5	"
23	"	2 to 3 "	8, or 34.7	"
33	"	3 to 4 "	12, or 36.3	"
22	"	4 to 5 "	9, or 40.9	"
17	"	5 to 6 "	10, or 58.8	"
21	"	6 to 7 "	9, or 42.8	"
19	"	7 to 8 "	13, or 68.4	"
10	"	8 to 9 "	6, or 60.0	"
65	"	9 to 15 "	38, or 58.4	"

For the cutaneous method, v. Pirquet reports reactions according to age in 988 children, as follows:

	Months.			Years.						Total.
	0–3	3–6	6–12	1–2	2–4	4–6	6–10	10–14	14+	
All cases	147	64	67	86	127	101	182	100	112	988
Positive	—	3	11	21	47	54	106	68	100	407
Per cent.	—	5	16	24	37	53	57	68	90	41
Clinically non-tuberculous:										
Cases	147	50	59	65	92	58	111	64	37	693
Positive	—	—	2	1	11	11	39	35	26	125
Per cent.	—	—	3	2	13	17	35	55	70	18

N. B.—The actual totals are 986 cases instead of 988, with 410 (not 407) reactions. There are 683 (not 693) clinically non-tuberculous, with 125 positive reactions. S. v. R.

Like statistics, for both children and adults, presented by Petruschky[32] include 460 cases of all ages, in which the age frequency of cutaneous reactions to tuberculin is given below:

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[29] Klin. Jahrbuch. Ergänzungsband, Berlin, 1891, p. 657.

[30] Arch. f. Kinderheilk., 1906, xliii, 121.

[31] Revue de méd., 1908, xxviii, 359.

[32] Tuberculosis, 1908, vii, 155.

Age.	Cases.	Positive.	Per cent.	Negative.
6 to 9 days	12	0	0.0	12
1 to 6 years	22	11	50.0	11
7 to 14 "	148	114	75.0	34
15 to 20 "	69	63	86.0	6
21 to 30 "	137	123	87.0	14
31 to 40 "	56	52	87.0	4
41 to 76 "	16	13	81.0	3
	460	376	81.7	84

Engel and Bauer[33] also report their results in 280 children, positive cutaneous reactions occurring with progressive frequency as age advances, and varying from 13 per cent. in boys and 20 per cent. in girls, in the fourth year of life, to 56 per cent. in boys and 50 per cent, in girls between thirteen and fourteen years of age.

The relation of the percentage of positive reactions to the general frequency of infection, as revealed by autopsy, thus appears to be fairly constant. For more reliable evidence we require statistics of autopsy findings in cases which have been tested. Of such statistics I have found but comparatively little in literature, but have been able to collect 77 cases in which the conjunctival test was applied and in which the positive or negative results were confirmed in 70, or 83.33 per cent. If we exclude 5 cases in which, after negative result, autopsy revealed only obsolete tuberculous foci, and in which the reaction might not be expected to occur, the test proved reliable in over 88 per cent. of the cases. Of cases tested by the cutaneous method, I have found records of 214 which came to autopsy, in 184, or 85.98 per cent., of which the results were thereby confirmed. Finally, of 54 cases tested by subcutaneous injection, the results were proved in all.

Autopsy controls for the conjunctival method have been reported by Wolff-Eisner, Morelli,[34] Blum and Schlippe,[35] Damask, Massary and Weil,[36] Comby,[37] Bourget,[38] Raviart,[39] Hirschler,[40] Fritz Levy, Marie and Bourilhet,[41] Fehsenfeld,[42] and Goerlich;[43] for the cutaneous method by Aronade,[44] Massini,[45] Engel and Bauer, Regli,[46] Lemaire,[47] Gruener,[48] v. Pirquet, and Ziesche;[49] and for the subcutaneous method, by Mettetal,[50] France,[51] Mikulicz,[52] and Diehl.[53]

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[33] Berl. klin. Woch., 1907, xliv, 1169.

[34] Wien. klin. Woch., 1908, xxi, 83.

[35] Münch. med. Woch., 1908, lv, 60.

[36] Bull. d. l. soc. méd. d. hôp., November, 1907 (cf. Blum und Schlippe, l. c.).

[37] Soc. méd. des hôp., July 19, 1907 (cf. Dembinsky, Ztschr. f. Tuberkulose, 1908, xii, 138).

[38] Rev. méd. d. l. Suisse romande, 1907, p. 88 (cf. Blum und Schlippe, l. c.).

[39] Comp.-rend. soc. d. biol., 1907, lxiii, 506.

[40] Wien. med. Presse, 1907, xlviii, 1765.

[41] Comp.-rend. soc. d. biol., 1907, lxiii, 281.

[42] Münch. med. Woch., 1908, lv, 1373.

[43] Ibid., 1379.

[44] Med. Klinik, 1907, iii, 51 (cf. Wolff-Eisner, Beitr. z. Klin. d. Tub., 1908, ix, 64).

[45] Correspondenzblatt f. Schweiz. Aerzte, 1908, xxxviii, 359.

[46] Ibid., 361.

[47] Rev. d. l. tuberculose, n. s., 1908, v, 199.

[48] Wien. klin. Woch., 1908, xxi, 986.

[49] Berl. klin. Woch., 1908, xlv, 1168.

[50] Thèse de Paris, 1900.

[51] Transactions of the British Congress on Tuberculosis, 1901, London, 1902, iii, 106.

[52] Deut. med. Woch., 1891, xvii, 373.

[53] Diss. Freiburg im Breisgau, 1892.

The significance of tuberculin reactions has also been questioned, because, as shown by Matthes,[54] Freymuth,[55] Cabot,[56] and others, subcutaneous injection of peptones, albumoses, and the like induced fever and other constitutional phenomena in tuberculous and in non-tuberculous persons similar to those occasioned by tuberculin. It is to be observed, however, that such effects follow only the injection of doses much larger than those in which tuberculin is active, and, moreover, and this is of determining importance, such substances have not the selective action upon tuberculous tissue peculiar to tuberculin. In the earlier period of tuberculin therapy tuberculous patients at the Winyah Sanitarium were frequently injected with unplanted glycerin-bouillon solutions, and while fever often resulted, no focal reaction was ever observed in visible tuberculous affections of mucous membranes, nor in the lungs so far as could be determined by auscultation.

On the other hand, focal reaction has been observed to follow diagnostic injections of tuberculin with such frequency, in our experience at the Winyah, that we have long considered this as of much greater diagnostic import than the general symptoms of fever, malaise, etc. Among 23 cases with positive reaction to diagnostic injection of tuberculin, given in the Institution in 1903 and 1904, focal reaction was unmistakable in 21. In the other two the previous presence of moist rales made differentiation of the local phenomena doubtful. The significance of focal reactions to tuberculin has also been pointed out by Neisser,[57] Maragliano,[58] Schwalbe,[59] and others.

In the production of fever reactions in the tuberculous, also by subcutaneous injection of bacterial proteids other than those derived from the tubercle bacillus, as shown, for example, by Feistmantel[60] with Streptothrix farcinia, by Klemperer,[61] and by Buchner and Roemer with proteins of Bacillus pyocyaneus, there is nothing surprising if the dosage is sufficient; and, as Feistmantel himself says, there is nothing which acts in its injection in minimal doses upon the tuberculous organism as does tuberculin.

The work of Irimescu[62] with paratuberculin prepared from Moeller's Timothy bacillus for conjunctival test (alcoholic precipitate), with which he obtained 44 positive reactions to first instillations out of 45 surely tuberculous cases, is to be accepted rather as evidence of the specific nature of the test than otherwise, since it illustrates the principle of group reaction. Neither does Irimescu interpret his observations as showing more than the close relationship existing between tuberculins and paratuberculins.

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[54] Deut. Arch. f. klin. Med., 1894, liv, 39.

[55] Diss. Erlangen, 1898.

[56] Journal of the Boston Society of the Medical Science, January, 1899.

[57] Klin. Jahrb. Ergänzungsband, Berlin, 1891, p. 418.

[58] Riforma medica, 1891 (cf. Münch. med. Woch., 1891, xxxviii, 149).

[59] Berliner Klinik, January, 1391, No. 31.

[60] Centralbl. f. Bakt., 1904, xxxvi, 282.

[61] Ztschr. f. klin. Med., 1892, xx, 165.

[62] Revist. Stiintel. med., 1907, Nos. 7 and 8 (cf. Centralbl. f. inn. Med., 1908, xxix, 87).

Finally, Fernand Arloing[63] believes he has supplied positive proof of the non-specific nature of the reaction. Two horses which had been used to obtain antidiphtheritic serum reacted positively, as did also two horses treated with tetanus toxin, while in untreated horses the reaction was negative, but appeared after five weeks of antidiphtheritic immunization. This author's results lack confirmation, and in controversion thereto, Calmette and Guérin[64] report entirely negative results in 23 horses, 8 of which were immunized against diphtheria, 8 against tetanus, and 7 were non-immune By the cutaneous method Entz[65] has obtained reactions in tuberculous adults and children to toxins other than tuberculin, as diphtheria, pyocyaneus and paratyphoid, in about 50 per cent. of cases.

To his denial, based upon these results, of the specific nature of the tuberculin test von Pirquet replies that, on the one hand, it has been shown for some toxins (mallein, leprolin, vaccin, tuberculin) that the organism will only then react to them if there has been a previous infection with the reciprocal microörganism; that, on the other hand, with other toxins (tetanus, diphtheria) such a previous infection ("acquaintance") is not necessary or essential to the reaction. These facts, he says, do not invalidate the specific nature of the cutaneous tuberculin test.

That non-specific protein substances are incapable of causing conjunctival reactions, Roepke ascertained in 25 tuberculous patients by instilling a 5 per cent. solution of glycerin bouillon which had first been condensed to one-tenth of its volume and then diluted. No effect was produced. I have also instilled a control preparation consisting of a 1 per cent. solution of the alcoholic precipitate of concentrated glycerin-bouillon into the conjunctival sac in 15 cases, 8 of which had previously given positive reactions to tuberculin, the same eye being used, without in a single instance observing the slightest influence, either general or local.

On the other hand, I have observed in several early cases of apex localization a focal reaction to occur simultaneously with the conjunctival reaction; the stethoscopic signs became distinctly intensified, and crepitation was heard where it had before been absent. Roe[66] also reports a case tested by the conjunctival method in which the occurrence of focal reaction in the lung cleared up the diagnosis, which had before been doubtful.

This would indicate that the tuberculous focus is concerned in the reaction. I cannot believe, therefore, that the latter depends upon the local formation of antibodies alone. With the minimal doses in which tuberculin is thus applied, 1 to 4 mg. (exceptionally), according to the strength of solution employed, part of which is, moreover, often not even retained in the conjunctival sac, it is not conceivable that enough would be absorbed into the circulation to produce manifest and recognizable focal reaction in a majority of cases, as is so frequently observed after subcutaneous injection of tuberculin.

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[63] Comp.-rend. soc. d. biol., 1908, lxiv, 722.

[64] Ibid., 889.

[65] Wien. klin. Woch., 1908, xxi, 379.

[66] Brit. Med. Jour., 1908, i, 443.

Further than this, for lack of space, I must refrain from entering into a consideration of the various theories which have been advanced in explanation of the conjunctival and cutaneous reaction, and of the divergent comparative results therewith obtained. So far as I can judge, none has as yet been formulated which satisfactorily meets all requirements and is entirely free from objection.

Among the specific aids in the diagnosis and prognosis of tuberculosis I have still to consider the serum reactions, and more particularly the agglutination reaction of Arloing and Courmont, with which my own experience is more extensive.

As regards the value of these methods, there still prevails a wide diversity of opinion. It was not long after Arloing and Courmont's first publication before the diagnostic significance which they claimed for the sero-agglutination of tubercle bacilli was disputed by other observers, because it was found that not only was the reaction inconstant in tuberculosis, but that it occurred occasionally in other affections, notably typhoid fever, and with the serum of healthy individuals.

Such experiences have caused many to deny that the test has any diagnostic value whatever, among whom may be cited Eisenberg and Keller[67] who noted but 13 per cent. more positive reactions in tuberculous than in non-tuberculous persons; also Dieudonné,[68] Beck and Rabinowitsch,[69] v. Gebhard and v. Torday,[70] de Grazia,[71] and lastly Wright and Douglas,[72] who state that the demonstration of the agglutinating power of serum affords no information of the presence or absence of tuberculosis.

Ferré,[73] Kinghorn,[74] Bendix,[75] Bandelier, and others find that in advanced cases of tuberculosis the reaction is often absent or is less pronounced.

Rumpf and Guinard[76] found the reaction positive in 84 per cent. of 107 cases, and Carrière[77] in 75 per cent. of second- and third-stage cases of phthisis. Berthelon[78] obtained 96 per cent. of positive results in pulmonary tuberculosis, many sera reacting in dilutions of 1 to 15, 1 to 20, and even some as high as 1 to 50. Hawthorn[79] reports 54 positive reactions out of 57 cases, and failed to obtain positive results in healthy individuals, although, in his experience, the reaction occurred in other diseases. Romberg[80] found no agglutination in 33 newborn infants, nor did Descos,[81] whether the mothers were tuberculous or not. Rosenberger[82] obtained complete reaction in dilutions of 1 to 1 in three, and of 1 to 3 in one, or in a total of 4 out of 39 newborn infants.

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[67] Centralbl. f. Bakt., 1903, xxxiii, 549.

[68] Deut. Militärärztl. Ztschr., 1900, No. 10.

[69] Transactions of the British Congress on Tuberculosis, 1901, London, 1902, iii, 153.

[70] Münch. med. Woch., 1902, xlix, 1171.

[71] Berl. klin. Woch., 1902, xxxix, 229.

[72] Lancet, 1904, ii, 1138.

[73] Ann. d. méd. et chir. infant., 1906, x, 648.

[74] Medical News, 1905, lxxxvii, 647.

[75] Deut. med. Woch., 1900, xxiv, 224.

[76] Deut. med. Woch., 1902, xxviii, 131.

[77] Comp.-rend. soc. d. biol., 1901, liii, 746.

[78] Congrès internat. d. l. tuberc., 1905, Paris, 1906, i, 359.

At the Winyah Sanitarium I have studied the subject for several years, applying the test on admission, and at intervals during treatment with specific remedies. Observations in 300 tuberculous cases which are complete show the following results:

	Cases.
On admission the test was negative in	20
Agglutination occurred in dilution of 1 to 5 in	49
" " " 1 to 10 in	86
" " " 1 to 15 in	21
" " " 1 to 20 in	50
" " " 1 to 25 in	57
" " " 1 to 30 in	7
" " " 1 to 40 in	4
" " " 1 to 50 in	6

In the same cases, on discharge the results were as follows: In 288 cases an increase of agglutinating power was observed under treatment with watery extract of tubercle bacilli. The serum of 63 agglutinated in dilutions of over 1 to 25, and not exceeding 1 to 100. Of these, 6 (or 9.35 per cent.) were apparently cured; the disease was arrested in 22, or 34.92 per cent.; improved in 27, or 42.85 per cent.; stationary in 6, or 9.35 per cent.; and had become worse in 2, or 7.4 per cent. The serum of 107 agglutinated in dilutions of over 1 to 100 and not exceeding 1 to 200. Of these, 41 (or 38.32 per cent.) were apparently cured; the disease was arrested in 51, or 47.66 per cent.; improved in 14, or 13.08 per cent.; stationary in 1, or 0.94 per cent.; and had grown worse in none. The serum of 90 agglutinated in dilutions over 1 to 200 and not exceeding 1 to 300. Of these, 73 (or 81.11 per cent.) were apparently cured; the disease was arrested in 15, or 16.76 per cent.; improved in 2, or 2.22 per cent.; stationary in none; had grown worse in none. The serum of 28 agglutinated in dilutions over 1 to 300 and not exceeding 1 to 500. Of these, 25 (or 85.7 per cent.) were apparently cured; the disease was arrested in the remaining 3, or 14.3 per cent. In the additional 12 cases a decline in agglutinating power was noted in 8, and a total loss in 4; all the 12 patients grew worse or died.

These observations are quite in accord with the experience of others. In 20 of our cases in which the diagnosis could be otherwise established no agglutinating power was present, while in 49 it did not exceed a dilution of 1 to 5. Again, in far advanced progressive cases the reaction either disappeared entirely or became progressively diminished.

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[79] Gaz. hebdom. d. méd. et d. chir., 1902, vii, 547.

[80] Münch. med. Woch., 1902, xlix, 89.

[81] Jour. d. physiol. et d. path. gén., 1903, v, 127.

[82] Zentralbl. f. inn. Med., 1904, xxv, 665.

Arloing and Courmont[83] subsequently to their earlier publications, decided that agglutination in dilutions below 1 to 5 should not be accepted as diagnostic, since the reaction was often present in healthy persons in such slight degree. My own experience would confirm me in the opinion that, in the absence of other definite evidence upon which to base a diagnosis, we should require a positive reaction in dilutions of not less than 1 to 10; this, because I have frequently observed reaction in lower dilutions in persons in whom suspicion of tuberculosis did not exist. With this qualification, of the 300 cases examined, 231, or 77 per cent., agglutinated in dilutions of 1 to 10 or higher, and in all the diagnosis was either sufficiently evident or could be determined by other means. In cases in which there is no sputum, or in which tubercle bacilli are absent, and in which the subjective symptoms and physical signs denote apex infiltration or catarrh, I have learned to depend upon the reaction when present in the higher dilutions as of positive determining value, and in such cases the tuberculin test may be dispensed with, its results in my experience always having confirmed those of the serum test.

The occurrence of agglutination in slight degrees in health does not detract from the value of the method in clinical practice. The facts that the reaction is frequently absent in the early period of the disease, that it is rarely missed when the disease is more developed, and is again diminished or lost toward the end, show that agglutinins form in the course of tuberculosis, as in other infectious diseases, in response to the absorption into the blood of specific toxins. The amount of agglutinins varies materially with the amount of specific toxins absorbed and the corresponding degree of response on the part of the organism. Hence it is that in the more developed disease we find the reaction most constantly present when the general condition and general resistance are still good. When these are greatly diminished in rapidly progressive cases the ability to respond is likewise lessened and the agglutinating power in consequence declines or is entirely lost.

The occurrence of the reaction in many healthy persons and in those affected with other diseases may be interpreted by assuming that latent foci exist in those who show slight degrees of agglutinating power, and in consequence of which they have acquired it.

The fact that the sera of newborn children are practically always negative, associated with the extreme rarity of congenital tuberculosis on the one hand, and on the other the great frequency with which latent and healed tuberculous foci are revealed at autopsy on the clinically non-tuberculous, renders more than probable the truth of such an explanation.

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[83] Congrès internat. d. l. tuberculose, 1905, Paris, 1906, 1, 332.

The greater comparative frequency with which the reaction occurs in cases of typhoid fever appears to bear an analogy to the recorded experiences with the tuberculin test in such patients. Thus, in a total of 70 typhoid fever cases, in which tuberculin was instilled into the conjunctival sac by various observers, positive reactions occurred in 20 or 28.37 per cent., as detailed below.

CONJUNCTIVAL TUBERCULIN TEST IN TYPHOID FEVER.

Author.	Cases.	Positive.	Negative	Preparation; Remarks.
Blum	18	4	14	9 had fever. Calmette's formula.
Austin and Gruenbaum[14]	8	0	8	Calmette's formula.
Clark[15]	14	7	7	T. old 0.5%. All fever cases.
Cohn, Sigism	11	6	5	T. old 1.0%. 1 positive case was paratyphoid; 4 afebrile.
Levy, Fritz	3	1	2	T. old. Hoechst. Convalescence.
Stadelmann and Wolff-Eisner	8	0	8	All negative to cutaneous.
Tice[16]	7	1	6	Tablet form.
Bourget	1	1	0	Autopsy negative as to tuberculosis.
	70	20 28.37%	50	

Again, according to Arloing and Courmont, typhoid fever patients show agglutinating power for the tubercle bacillus in 75 per cent. of cases.

From this Calmette and Guérin infer that the Eberth bacillus forms agglutinins which are capable of agglutinating both kinds of bacilli, but Arloing and Courmont claim that this occurrence is not due to the identity of the two agglutinins, nor to a parallel method of production. The serum of an animal, they say, may acquire a high agglutinating power for the Eberth bacillus after inoculation with this bacillus, without exhibiting the like characteristic for Koch's bacillus.

This question is an interesting one, and engaged my attention some ten years ago in a comparative study of the agglutinating power of the blood sera of normal individuals and of tuberculous patients in relation to the Eberth bacillus. In my own experiments I used for control serum from typical cases of typhoid fever, which was found to agglutinate completely the Eberth bacillus in dilutions of 1 to 10 in fifteen minutes. The sera of normal persons who had never had typhoid fever, and who were free from all suspicion of tuberculosis, showed no tendency to agglutinate the Eberth bacillus even after one hour. As compared with the normal and with typhoid sera, the sera of tuberculous patients with no history of typhoid fever showed beginning agglutination of Eberth's bacillus in fifteen minutes and well marked agglutination in thirty minutes in the same dilution.

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[14] Brit. Med. Jour., 1907, ii, 1907.

[15] Jour. Amer. Med. Assoc., 1908, l, 2061.

[16] Ibid., 1982.

The only explanation for these observations, and one which may be applied with as much reason to account for tuberculin reactions in typhoid fever patients in greater frequency than these occur in healthy persons, appears to lie in that of group reaction, even though the Eberth bacillus seemingly presents nothing in common with the acid-proof bacteria. However that may be, no definite conclusions are warranted.

In this consideration of specific aids in the diagnosis and prognosis of tuberculosis I have endeavored to show the comparative value of the various resources at hand.

The specific nature and value of tuberculin as a diagnostic agent does not appear to be refuted by the objections which have been raised against it. The minimal amounts in which it is active, the negative results obtained by all three methods of applying it in the newborn, the increasing comparative frequency of positive reactions with advancing age in their approximate harmony with autopsy findings in the clinically non-tuberculous as well as the tuberculous, the occurrence of focal reactions following subcutaneous injection and conjunctival instillation, all testify to its reliability.

To demand that either positive or negative results be confirmed with mathematical accuracy by actual autopsy findings would be unreasonable; nor has clinical medicine progressed to such a degree of precision in other respects.

As much may be said for the serum reactions. As for the various contradictions which have apparently arisen with regard to all the diagnostic measures which have been considered, and which are at present not explained, these are problems which may yet be solved in the future.

In clinical practice the occasion can seldom arise to enter so deeply into such questions. Persons who are in good health do not often consult a physician, nor would any but the most unconservative base a diagnosis upon a single isolated bit of evidence. In nonbacillary cases suspected of tuberculosis, when physical examination reveals abnormal conditions suggestive of the presence of a tuberculous affection, the tuberculin test as well as the serum reaction, or both, may safely be depended upon for confirmation in the vast majority of instances. One may be employed to supplement the other, and thus, taking all things into consideration, the patient is not likely to be placed at a disadvantage for want of a diagnosis.